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Date :	July 15, 2002
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MESSAGE:

Re: United States Patent Application No.: 09/515,276
Entitled: METHODS FOR TREATING DIABETES MELLITUS
Filed: February 29, 2000
Inventor: Marc R. Montminy
Client Ref. No.: S97037B
Our Docket No.: SALK650-4

ATTACHED IS THE **APPEAL BRIEF FILING**, IN TRIPLICATE, IN CONNECTION WITH THE ABOVE-REFERENCED PATENT APPLICATION.

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Attorney Docket No.: SALK1650-2
(888808.2763)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Marc R. Montminy

Title: METHODS FOR TREATING DIABETES MELLITUS

Appl. No.: 09/515,276

Filing Date: 02/29/2000

Examiner: D. Wortman

Art Unit: 1648

TRANSMITTAL FOR APPEAL BRIEF

Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is an Appeal Brief in the above-identified application.

[X] Applicant claims small entity status. See 37 CFR 1.27.

[X] Please charge Deposit Account No. 50-0872 in the amount of $160.00. A duplicate copy of this transmittal is enclosed.

[X] The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date: July 15, 2002

By _____

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PATENT
Atty. Docket No. SALK1650-2
(088802-2753)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Marc R. Montminy

Title: METHODS FOR TREATING DIABETES MELLITUS

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CERTIFICATE OF FACSIMILE TRANSMISSION
I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office, Washington, D.C. on the date below.

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July 15, 2002
(Date of Deposit)

APPEAL BRIEF

Commissioner for Patents
Washington, D.C. 20231

Sir:

Appellant (herein, "Appellant") submits this Appeal Brief in response to the Final Rejection of claims 1-7, 12 and 17. This Appeal Brief, submitted in triplicate, is accompanied by the requisite fee set forth in 37 C.F.R. § 1.17(c). If this fee is incorrect or if any additional fees are due in this regard, please charge or credit Deposit Account No. 50-0872 for the appropriate amount.

PATENT
Atty. Docket No. SALK1650-2
(088802-2753)

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Real Party in Interest

The real party in interest in this appeal is The Salk Institute for Biological Studies, which is the assignee of the present application.

Related Appeals and Interferences

Appellant is not aware of any related appeals or interferences that may have a bearing on the board's decision in the pending appeal.

Status of Claims

Claims 1-7, 12 and 17 were finally rejected by the Examiner on December 17, 2001. Appellant responded with an Amendment After Final on April 17, 2002. An Advisory Action issued on May 1, 2002 indicating that the Amendment was entered, a rejection under 35 U.S.C. § 112, second paragraph was withdrawn, and a rejection under 35 U.S.C. § 112, first paragraph was maintained. A Notice of Appeal for claims 1-7, 12 and 17 was timely filed by Appellant on May 15, 2002. The text of claims 1-7, 12 and 17 are attached hereto as Appendix A.

Status of Amendments

All Amendments have been indicated as entered.

Summary of The Invention

Appellant discovered that intracellular interaction exists between cAMP responsive transcriptional activator ("CREB") and CREB binding protein ("CBP"), a protein that binds to the phosphorylated (i.e., activated) form of CREB and mediates cAMP responsive transcription. From this discovery, Appellant devised methods of identifying compounds that would act as inhibitors of this interaction and appreciated that such compounds would be useful in the treatment of diabetes mellitus (see, e.g., Summary of the Invention). Thus, the present invention relates to methods for treating individuals with diabetes mellitus using a compound that inhibits the interaction between the CREB and CBP. Claims 12 and 17 each specify a method by which the inhibitory compounds are identified.

At the time the instant patent application was filed, is was not known that CREB and CPB interaction was necessary for gene transcription mediated by a number of activators that mediate their activity through the general intracellular mediator, cyclicAMP.

Issues

1. Whether a prima facie case of lack of enablement has been established by the Examiner without providing evidence that disputes or otherwise contradicts the inventive mechanism of action for treating diabetes mellitus.

2. Whether Appellants have overcome a prima facie case for lack of enablement assuming *arguendo* that such case has been established.

Grouping of Claims

Claims 1-7, 12 and 17, all directed to a method of treating diabetes mellitus, all stand or fall together.

Argument

The rejection of claims 1-7 and 12 and 17 for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, is respectfully submitted to be in error for the following reasons.

Appellant respectfully submits that the Examiner has failed to establish a *prima facie* case of lack of enablement. First, the Examiner has improperly required Appellant to demonstrate that the inventive mechanism of action was accepted in the art prior to filing of the application. Such requirement is clearly improper as it is directly in conflict with the novelty requirements of the patent statute. Moreover, the requirement would be against the public policy underlying the patent statute because its impact would be to bar original discoveries based on new mechanisms of treatment.

Moreover, the rejection, which the Examiner initially predicated on the fact that Appellant's mechanism of action was not disclosed in the Merck Manual (a listing that describes only previously existing treatment modalities), has been demonstrated by Appellant to lack all relevance to the question of enablement. Appellant also has cited to post filing publications in prestigious journals by the inventor describing the inventive methods and asserting its use in treating diabetes mellitus.

The Examiner now admits that the Mayr and Herzig articles "provide some indication that CREB:CBP interaction may be relevant to some aspects of diabetes."

Advisory Action, 05/01/02, p. 3, lines 1-2. The Examiner also appears to accept that the screening method for identifying inhibiting compounds described in the application is enabled. Nonetheless, the Examiner continues to insist that the diabetes field is unpredictable and that clinical data are required to demonstrate that " a compound exists that has both the binding-inhibitory effect required and is effective to treat a human with diabetes." Final Office Action, 12/17/01, p. 3, lines 17-20.

By offering no credible scientific reasoning for why Appellant's method of diabetes mellitus treatment will not work and in fact discounting evidence to the contrary (the Mayr and Herzig references), the Examiner has not only failed to meet the burden on the Patent Office to establish a *prima facie* rejection for enablement, but has improperly shifted that burden onto the Appellant. This ignores the settled law which indicates that the Examiner carries the initial burden and must explain why the truth or accuracy of any statement in the specification is doubted. The conclusion by the Examiner that the claims are not enabled, therefore, is wholly without basis in the law.

For these reasons, Appellant respectfully requests that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn or reversed.

Burden and requirement for establishing a prima facie rejection for lack of enablement of 35 U.S.C. § 112, first paragraph

The standard for determining enablement is whether the specification as filed provides sufficient information to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather

whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Under Patent Office practice, a patent specification is considered to be in compliance with the enabling requirement of § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein. Thus, the Examiner carries the initial burden to substantiate a rejection for lack of enablement. In re Marzocchi, 439 F.2d 220, 223-24 (CCPA 1971). In accordance with the burden, the Patent Office must explain why the truth or accuracy of any statement in the specification is doubted and "back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." Id.; see also, In re Richard Sichert, 566 F2.d 1154, 1161 (CCPA 1977)) ("The PTO has cited to no evidence or reference that contradicts or is inconsistent with any supporting statement of the disclosure.").

By failing to provide any evidence that disputes or otherwise contradicts the inventive mechanism of action for treating diabetes mellitus, the Examiner has failed to meet his/her burden of stating a prima facie case of lack of enablement.

1. The Fact that Appellant's method or mechanism of action is not discussed in Merck Manual is NOT Relevant to the Question of Enablement.

Appellant respectfully disagrees with the Examiner's assertion that the enablement rejection is supported by the fact that Appellant's method of treatment is

not discussed in the section of the Merck Manual, 17th edition, that addresses treatment of diabetes (citing the Merck Manual pages 174-176). Such evidence would only be relevant to the question of enablement if it would be shown that the Merck Manual were a reliable source for the latest in diabetes treatment methods and mechanisms of action. The Examiner has the burden to provide this essential evidence for relevance but has offered nothing.

Although Appellant has no duty to cite contrary evidence on this account since the Examiner has the burden, and the Examiner's assertion remains unsubstantiated, Appellant respectfully submits that the Merck Manual is not probative evidence of non-enablement. The Merck Manual discusses well established methods of diabetes treatment, mainly treatment using insulin, sulfonylureas, and certain anti-hyperglycemic drugs; The Manual, however, is silent as to new methods of diabetes treatment as evidenced by its failure to mention any of a larger number of recently patented diabetes treatment methods (a search for "diabetes," "treat" and "method" as claim terms identified 89 issued U.S. patents; a random sampling of these showed that many are directed to new methods of diabetes treatment that are not mentioned in the Merck Manual) (See e.g., U.S. No. 6,323,314 – thiophene derivatives; U.S. No. 6,300,349 N-substituted 2(1H) pyridones; U.S. No. 5,888,507 – antibody to VLA-4; U.S. No. 5,834,032 – zinc cation, anion and cyclo-Hisporo; U.S. No. 6,146,653 - amylin agent; U.S. No. 5,541,192 substituted sulfonamides; U.S. No. 5,691,386 - triterpenoids; 5,674,900 - terpenoids, U.S. No. 5,700,795 -muscarinic receptor antagonists; and U.S. No. 5,561,110 - carnosine).

Accordingly, failure to be discussed in the Merck Manual is a fact entirely without moment to the present rejection and cannot be used by the Examiner to support a prima facie rejection for enablement. The Examiner now appears in more recent communications to have backed off from the significance afforded to the Merck Index when it was first asserted. Nonetheless, Appellant is compelled to argue the merits of this citation since the Examiner has not yet acknowledged for the record that the Merck Manual does not support a *prima facie* rejection for lack of enablement.

2. The Mayr and Herzig References Do Not Support the Rejection

Mayr et al. ("Transcriptional Regulation of the Phorphorylation-Dependent Factor CREB" Molec. Cell Biol., 2:599, 2001) and Herzig et al. ("CREB Regulates Hepatic Gluconeogenesis Through the Coactivator PGC-1" Nature 413:179-183, 2001), both of record in the case, do not support the rejection for lack of enablement as alleged. Rather, these articles provide additional evidence that the claimed invention is enabled as described.

Mayr et al. (Mayr) is a review article published in the prestigious journal, Nature. Mayr makes clear in the Abstract to the article that CREB is involved in control of glucose levels. Mayr, p. 599 (stating that CREB "functions in glucose homeostasis"). Mayr also describes that the mechanism by which CREB controls glucose homeostasis involves phosphorylation of CREB at Ser133, which promotes complexing with the transcriptional co-activator CBP. Mayr, p599, left column and Figure 1a. These conclusions are consistent with Appellant's disclosure teaching involvement of CREB-CBP complex in diabetes. Furthermore, Herzig et al. ("Herzig") reports that CREB

controls glucose homeostasis through expression of gluconeogenic enzymes via the transactivator, PGC-1. Herzig also used normal and diabetic animals to prove that a reduced CREB activity causes fasting hyperglycemia in vivo, a result that Herzig states "is correlated with Type II diabetes." Herzig, page 179 (Abstract).

Therefore, both the Mayr and Herzig articles support enablement of Appellant's disclosure. In fact, the Examiner in the most recent communication appears to admit that the teachings of these disclosures are consistent with enablement (stating that the Mayr and Herzig articles "provide some indication that CREB:CBP interaction may be relevant to some aspects of diabetes." Advisory Action, 05/01/02, p. 3, lines 1-2). The Examiner, however, discounts this admission by asserting that the articles show that "this is an area inviting further research." *Id.* No scientific reasoning, however, has been offered to support this assertion.

3. The Rejection Fails to Raise Any Scientific Reasoning For Why Appellant's Method is not Enabled as Described.

The Examiner has offered no acceptable evidence or reasoning (scientific or otherwise) that is inconsistent with Appellant's method for treating diabetes by administering a compound that inhibits binding of CREB to CPB. There also is no support for the Examiner's assertion that the specification lacks factual evidence supporting enablement including a working example that a compound that inhibits or disrupts the binding of CREB or CPB provides any beneficial effect in treating diabetes mellitus. The Examiner admits that the specification provides an enabling method for identifying a compound that inhibits CREB-CPB interaction, and Appellant further points

out that the specification provides substantial guidance in compound formulation and in vivo dosage (see pages 19-20). Although Appellant's disclosure does not include in vivo experimental data, there is no per se requirement to have human clinical data to enable a method of therapy. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993) ("[I]t is irrelevant whether the teaching of the patent is provided through broad terminology or illustrative examples"). The specification is presumed under the law to be enabling and the Examiner has failed to meet his/her burden to set forth credible reasoning for why inhibitory compounds selected by Appellant's method would not be useful in treating diabetes.

In view of the above, it is respectfully submitted that the Office Action fails to state a prima facie case for the rejection because it is not founded on sufficiently "acceptable evidence or reasoning which is inconsistent" with Appellant's method. In re Marzocchi, 439 F.2d 220, at 223-24 (CCPA 1971). Accordingly, Appellant respectfully requests that the rejection be withdrawn or reversed.

Appellant has overcome a prima facie case for lack of enablement assuming arguendo that such case has been established.

The Examiner carries the initial burden to state a prima facie rejection for lack of enablement, but once that is done, the burden shifts to Appellant to rebut this conclusion by presenting evidence to prove that the disclosure in the specification is in fact enabling. In re Endyne, 480 F.2d 1364, 1376 (CCPA 1973). Materials submitted to prove enablement must be factual evidence such as patents, publications and affidavits. Id. References published after the filing date of the application in question

may be used in this regard if the purpose is to prove the accuracy of a statement in the specification. See In re Marzocchi, 439 F.2d at 224, n.4.

Although it is respectfully submitted that the Examiner has not met his/her burden, even if one assumes *arguendo* that such burden has been met, the evidence of record is more than sufficient to prove that the specification is enabling. As admitted by the Examiner, the specification teaches methods to identify a compound that inhibits the interaction of CREB with CBP. Included is a description of various cell lines to use and expression vectors to express the interacting proteins in the form of a functional bioassay. Inhibiting compounds are described and include, for example, fragments of CREB or CBP, or antibodies that bind to epitopes of CREB or CBP that are involved in the interaction (see page 13-15). The working examples of the specification provide further enabling support for compound selection methods. With respect to diabetes treatment, for compounds which meet the inventor's criteria, the specification provides a general description of suitable routes of administration, methods of formulation, and dosing, the latter including concentration ranges (page 17-18).

To further support Appellant's position that the description in the specification is indeed, enabling, Appellant cites to peer reviewed scientific publications. As discussed above, Mayr demonstrates that CBP/CREB interaction is required to transcriptionally activate CREB, while Herzig demonstrates that transcriptionally activated CREB is involved in diabetes mellitus. The Mayr and Herzig articles, published in peer-reviewed and prestigious scientific journals, strongly evidence that Appellant's patent disclosure is enabling and overcomes any suggestions to the contrary, such as the failure to be

mentioned in the Merck Manual. The Examiner's failure to consider these references as evidence because they were published after the filing date of the instant patent application and use methods to obtain results that go beyond those instantly disclosed is without basis in the law. These references are relied on to prove the truth of statements in Appellant's disclosure that disruption of CREB-CBP interaction can be used to treat diabetes rather than to supplement the disclosure itself. See In re Marzocchi, 439 F.2d at 224, n.4 (indicating that references which are not prior art can be used to rebut a prima facie case for lack of enablement if the "question would be regarding the accuracy of a statement in the specification, not whether that statement had been made before.").

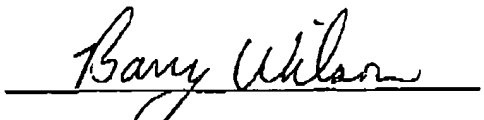
Therefore, because the claimed invention is supported by an enabling disclosure that meets the standard under 35 U.S.C. §112, first paragraph, Appellant respectfully requests that the rejection be withdrawn or reversed.

Conclusion

For the reasons discussed above, the instant claims are in condition for allowance, and Appellant respectfully request that the rejections be withdrawn or reversed.

Respectfully submitted,

Date: July 15, 2002

By 

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PATENT
Atty. Docket No. SALK1650-2
(088802-2753)

Appendix A: Text of the Claims Involved in the Appeal

1. A method for treating diabetes mellitus, said method comprising contacting an individual with an effective amount of a compound which inhibits binding of CREB to CBP.

2 A method according to claim 1 wherein said treatment of diabetes mellitus ameliorates hyperglycemia.

3. A method according to claim 2 wherein gluconeogenesis is modulated.

4. A method according to claim 3 wherein transcription of PEPCK is inhibited.

5. A method according to claim 2 wherein transcription of glucagon gene is inhibited.

6. A method according to claim 1 wherein said individual is a human.

7. A method according to claim 1 wherein said contacting is carried by oral, intravenous, subcutaneous, intramuscular or intracutaneous mode of administration.

12. A method for treating diabetes mellitus, comprising contacting an individual with an effective amount of a compound which disrupts a complex comprising cyclic AMP response element binding protein (CREB) and CREB binding protein (CBP), said compound identified by a method comprising:

(a) contacting a modified host cell with a test compound, wherein said modified host cell comprises:

a first fusion protein comprising a GAL4 DNA binding domain, operatively associated with the kinase-inducible domain (KID) of CREB,

a second fusion protein comprising an activation domain, operatively associated with the CREB binding domain (KIX) of CBP, and

a reporter construct comprising a GAL4 response element operatively linked to a reporter gene; and

(b) selecting those test compounds which cause reduced expression of the reporter gene product, wherein said compounds are identified as disrupting a complex comprising CREB and CBP.

17. A method for treating diabetes mellitus, comprising contacting an individual with an effective amount of a compound which disrupts a complex comprising cyclic AMP response element binding protein (CREB) and CREB binding protein (CBP), said compound identified by a method comprising:

(a) contacting a modified host cell with a test compound, wherein said modified host cell comprises:

a first fusion protein comprising an activation domain, operatively associated with the kinase-inducible domain (KID) of CREB,

a second fusion protein comprising a GAL4 DNA binding domain, operatively associated with the CREB binding domain (KIX) of CBP, and

a reporter construct comprising a GAL4 response element operatively linked to a reporter gene; and

(b) selecting those test compounds which cause reduced expression of the reporter gene product, wherein said compounds are identified as disrupting a complex comprising CREB and CBP.